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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,568	04/08/2004	Jose Remacle	VANM212.001DV1	1710

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
03/20/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/821,568	REMACLE ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30,33-38,40,42 and 43* is/are pending in the application.

4a) Of the above claim(s) *1-26 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-30,33,35-38,40,42 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/18/2007 and 8/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Status

Applicants' response of December 14, 2007, to the non-final action dated July 13, 2007 has been entered. Claims 1-30, 33-38, 40, 42 and 43 are pending in the application. Claims 27, 28, 36 and 40 have been amended. Claims 31, 32, 39 and 41 have been cancelled and claims 42 and 43 newly added. Claims 1-26 and 34 remain withdrawn from consideration, without traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 27-30, 33, 35-38, 40, 42 and 43 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed 8/2/2007 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been fully considered, as the reference of Brand et al. was not present in the instant application. Applicant is required to provide a copy of the missing reference to be considered by the examiner.

Response to Rejections - 35 USC § 112- Second Paragraph

Claim 40 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite, in the previous office action dated July 13, 2007. Applicants' cancellation of the claim renders the rejection moot. Thus, the rejection is hereby withdrawn.

New Claim Rejections - 35 USC § 112- New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 27, 36, 42 and 43 are newly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR §1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Comment [a1]: For RCE practice, we do not make the RCE Final if new rejections are added, particularly new matter rejections. Look at it this way, if they had filed this as an after-final you would not have entered it and so the RCE gives them the opportunity for additional consideration.

Claims 42 and 43 recite the limitation: "wherein the spacer comprises a double-stranded DNA sequence between about 50 and about 250 base pairs". The instant specification is devoid of any such description for the claim limitation. Applicants state that support for the amendment can be found in the specification at paragraphs [0034], [0050] and [0109]. However, no specific support for the claimed "about 50 and about 250 base pairs", is present. The cited paragraphs recite spacers of "at least 50, 100, 150 or 250 base pairs", "between 50 and 250 base pairs", and "50, 100, 150 and 250 bp". Thus, the disclosure of the cited paragraphs is not synonymous with the limitation of the instant claim.

Thus, at the time the application was filed, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of spacers comprising "double-stranded DNA sequence between about 50 and about 250 base pairs", as claimed.

This is a new matter rejection.

Response to Claim Rejections - 35 USC § 103

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 27-29, 31-33 and 36-41 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Peterson et al. (U.S. Patent No. 5,563,036, filed Apr. 29, 1994) in view of Hibma et al.

(Nucl. Acids Res. 22:3806-3807; 1994), and further in view of Kaltschmidt et al. (Biol. Chem. Hoppe-Seyler 376:9-16; 1995). Applicants' cancellation of claims 31, 32, 39 and 41 renders their rejection moot. The rejection set forth on pp. 3-6 of the previous office action dated July 13, 2007 is maintained for claims 27-29, 31-33, 36-38 and 40, and further applied to new claims 42 and 43, for reasons of record.

Applicants disagree with the rejection, and citing paragraphs 8 and 9 of the rule 1.32 Declaration by Applicant Jose Remacle, argue that Applicants unexpectedly discovered that activated transcription factors present at very low amounts in a cell or cell lysate can be detected in a binding assay combining double- stranded DNA sequences comprising the binding sites for the transcription factors and a spacer comprising at least a double-stranded nucleotide sequence of at least 50 nucleotides where the nucleotide sequence of the spacer is not present in the tested cell. Concluding that the data presented in the Declaration show that the kit as claimed is sensitive and specific (see paragraph 9). The high sensitivity obtained with the present kit allows the use of non radioactive detection means, and provides advantages over the method of Peterson et al. Applicants' argument s have been fully considered, but are not found persuasive.

It is noted that "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d535, 538, 152 USPQ 602, 604 (CCPA 1967). The fact that a spacer sequence of at least 50 nucleotides provides for the detection of low amounts of transcription factors in a cell lysate is not surprising, nor unexpected in view of the teachings of Peterson et al. who describe their double stranded nucleic acid as most preferably between about 27 and 50 bp (lines 24-28, column 6). Further, teaching that the detection method may be by liuminescence or indirect, such as an epitope tag of an enzyme (lines 11-14, column 6).

The previous office action quoted Peterson et al. as stating the nucleic acid contains at least a portion of which is common to the gene regulatory region to which the transcription factor normally binds, the binding site portion constituting between 4 and 8 nucleotides (column 6, lines 39-48). Thus, the remaining sequence length would constitute a spacer sequence. Applicants state: "It is understood from the reading of this sentence that the remaining sequence is a sequence adjacent to the portion of gene or gene regulatory region to which the native

transcription factor binds, thus the remaining sequence is part of the gene or gene regulatory region." Concluding that a nucleotide sequence of 18 to 250 bp naturally involved in the regulation of the transcription of the gene, and cannot be used to reach specific transcription factor detection." Applicants refer to the sequence of 46 bp exemplified in Peterson et al., designed to bind NFkB (col. 13, lines 10-12), and state that a search of the sequence indicated that other factor binding sites were found to overlap these sites. Further arguing that Peterson et al. neither suggest nor mention the use of a spacer comprising a double- stranded nucleotide sequence which is at least 50 nucleotides long and which is not found in the cell containing the activated transcription factors to assay.

Such is not found persuasive, because as shown on the record, Peterson et al. describe double stranded oligonucleotides of 50 bp as well as nucleic acids of 250 bp. Moreover, Applicants' interpretation of Peterson's teachings, in that the entire double stranded nucleic acid segment is understood to be part of a gene regulatory region in a cell, is incorrect. Peterson et al. state that "The nucleic acid has a sequence at least a portion of which is common to the gene or gene regulatory region to which the native transcription factor normally binds...this binding portion of the nucleic acid constitutes at least about 4, preferably about 6, more preferably about 8 nucleotides." (lines 38-48; column 6). Peterson et al. further state that the nucleic acid may include retroviral transcription factor binding sites (lines 26-29; column 6), and additionally disclose Epstein Barr virus, HSV VP-16 and HIV TAT binding assays comprising sequences not present in a cell.

It is therefore clear from the teachings of Peterson et al. that the non-binding portions of the nucleic acid may be comprised of any sequence. Peterson et al. exemplify a total of 75 different nucleic acid sequences. Applicants' have attempted to dismiss the teachings of Peterson et al. by reference to a single oligonucleotide sequence exemplified for NFk-B binding. As stated in MPEP 2112: "Even if a reference discloses an inoperative device, it is prior art for all that it teaches." *Beckman Instruments v. LKB Produkter AB*, 892 F.2d 1547, 1551, 13 USPQ2d 1301, 1304 (Fed. Cir. 1989).

Applicants argue that there is no teaching or suggestion in Peterson et al. of a kit comprising a second labeled antibody directed against the primary antibody or the specific

hypervariable portion thereof, wherein said second labeled antibody is conjugated with an enzyme. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The limitation argued as absent in Peterson et al. is provided by Hibma et al., wherein using double-stranded biotinylated oligonucleotides attached to streptavidin coated plates, the authors describe the use of a mouse monoclonal antibody to detect the HPV E2 protein in their assay using a peroxidase labeled anti-mouse polyclonal antibody (second column, p. 3806). Further the limitation of a kit comprising a spacer comprising double stranded nucleotide sequence of at least 50 nucleotides is provided by Peterson et al. and is not required as a teaching of Hibma et al.

Applicants additionally argue that neither Peterson nor Hibma suggest specifically detecting activated forms of transcription factors. Such is not found persuasive, because the deficiency is obviated by the teachings of Kaltschmidt et al. describe a monoclonal antibody that selectively recognizes the activated form of the p65 NF-kB transcription factor in cultured cells (Title and Abstract).

Claims 27, 30 and 35 stand newly rejected under 35 U.S.C. §103(a) as being unpatentable over Peterson et al. (U.S. Patent No. 5,563,036, filed Apr. 29, 1994), in view of Hibma et al. (Nucl. Acids Res. 22:3806-3807; 1994), and further in view of Kaltschmidt et al. (Biol. Chem. Hoppe-Seyler 376:9-16; 1995), and Church et al. (U.S. Patent No. 6,326,489, filed Aug. 5, 1997). The rejection set forth on p. 6 of the previous office action dated July 13, 2007 is maintained for claims 27, 30 and 35, for reasons of record.

Applicants disagree with the rejection, arguing, the references of Peterson, Hibma and Kaltschmidt do not teach all of the claim limitations of a kit comprising a solid support comprising a DNA sequence which binds an activated transcription factor present in a cell and a spacer comprising a double-stranded nucleotide sequence of at least 50 nucleotides which is not present in said cell. In the context of microarrays, it is very important that the spacer sequence does not belong to the genome of the cells being assayed to avoid binding of the assayed, but

more importantly of other transcription factors to the spacer sequence. Applicants' arguments have been fully considered, but are not found persuasive.

Applicants are referred to the response provided in the foregoing.

Thus, the rejection of claims 27-30, 33, 35-38 and 40 are maintained, and further applied to new claims 42 and 43, for reasons of record and the commentary provided above.

Conclusion

Claims 27-30, 33, 35-38, 40, 42 and 43 are not allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. The claims are drawn to the same invention claimed earlier in the application and would have been finally rejected on the grounds and art of record in the next Office Action if they had been entered earlier in the application. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner, Art Unit 1633

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